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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,534	06/18/2001	Bryan John Smith	1300-1-008	5753

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,534	SMITH, BRYAN JOHN	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The following action is a supplemental office action with new Office Action Summary attached hereto to clarify the finality and is identical to the action mailed 7/1/04.

Applicant's amendment filed 3/8/04 is acknowledged and has been entered.

Claims 14-20 are pending.

2. Applicant is reminded of Applicant's election of a hybrid protein having the antigen-binding antibody fragment linked to an albumin molecule or fragment thereof, the linkage being by a bridging molecule between the thiol groups of a cysteine residue that is present in the antibody and another such residue present in albumin at position 34, in the amendment filed 6/16/03.

Claims 14-20 read upon the elected species and are currently being examined.

3. Given Applicant's amendment of claim 14, for the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the PCT application PCT/GB99/03747, i.e., 11/10/99.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 14-20 stand rejected under 35 U.S.C. § 103(a) as obvious US Patent No. 6,350,431 in view of Peters (IDS reference "AT") and the known facts disclosed in the specification on page 27 at lines 9-13.

US Patent No. 6,350,431 discloses a polymeric targeting radioactive immunoreagent/pharmaceutical compositions thereof, comprising a metal radionuclide ion (i.e., an effector group as disclosed on page 9 of the instant specification at lines 5-14), a linking group and an immunoreactive group (i.e., vector) which is attatched through a linking group to the polymer (especially column 21 at lines 45-50). US Patent No. 6,350,431 further discloses that the immunoreagent can be an antibody, or a fragment thereof such as Fab or Fab'2 (especially column 25 at lines 6-11, column 23 at lines 4-8 and lines 44-54), that the linking group may be optionally substituted hexylene (especially column 43 at line 27-67, column 44 at lines 1-19 and column 45 at lines 49-60) and that the linking group may comprise

albumin (especially column 48 at lines 12-13). US Patent No. 6,350,431 discloses that the vector reactive group can be selected from a sulfhydryl group such as a cysteine sulfhydryl group commonly found on a protein or other biological molecule (especially paragraph spanning columns 27 and 28).

US Patent No. 6,350,431 does not disclose that the indirect linking is between the thiol groups of a cysteine residue present in the antibody and another present in the albumin at position 34.

Peters teaches the presence of a free cysteine in albumin (especially paragraph spanning pages 164 and 165).

The known facts disclosed in the specification on page 27 at lines 9-13 are that serum albumin has one cysteinyl residue that is not engaged in a disulphide bond, i.e., at position 34 in mature human albumin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made with regard to the immunoreagent disclosed by US Patent No. 6,350,431 to have attached the linking (bridging) molecule at position 34 in the albumin since the cysteine is free and the remainder of the cysteines are involved in intrachain disulfide bonds as taught by Peters.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce a pharmaceutical immunoreagent such as the one disclosed by US Patent No. 6,350,431 wherein the native structure of the albumin carrier was retained by non-disruption of intrachain disulfide bonds as taught by Peters. Claim 15 is included in this rejection because the linking molecules disclosed by US Patent No. 6,350,431 range from "around 10A[angstroms] to around 20 A[angstroms] in length" recited by the instant claim. Claim 17 is included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the Fab at the CH1 carboxy terminus to include the cysteine involved in the interchain disulfide bond of the intact antibody in order to utilize the cysteine in disulfide binding without disrupting intrachain disulfide bonds.

Applicant's arguments in the amendment filed 3/8/04 have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on page 7 (at the last paragraph) through page 9 through the first two full paragraphs.

It is the Examiner's position that US Patent No. 6,350,431 not only discloses that albumin can be a linking group, but that it also a polymer and a chelating agent (column 21 at lines 30-34 and column 46 at lines 8-39, column 50 at lines 35-62). US Patent No. 6,350,431 further discloses that albumin is most preferred (column 50 at lines 58-62) and that the polymeric

targeting immunoreagent comprises a metal radionuclide ion, a chelating agent in a linking group of the polymer and an immunoreactive group which is attached through a linking group to the said polymer (column 21 at lines 30-50), i.e., a metal ion linked to a chelating agent such as albumin linked through a linker such as hexylene or substituted hexylene to an antibody fragment. It is the Examiner's further position that one of ordinary skill in the art at the time the invention was made would have been motivated to use the free cysteine at position 34 of human serum albumin taught by Peters because it is unpaired, and one of ordinary skill in the art would have been motivated to use albumin in native conformation where an antigen-binding antibody fragment rather than an intact antibody was being used because Peters teaches that albumin in native conformation is an abundant serum protein with a half-life in circulation of about 19 days, similar to that of the IgG isotype antibody (known to one of ordinary skill in the art at the time the invention was made, as evidenced by admitted prior art Waldeman et al 1969 (IDS reference "AZ"), page 3 at lines 14-16 of the instant specification).

6. Claims 14 and 17-20 stand rejected under 35 U.S.C. § 103(a) as obvious US Patent No. 4,751,286 in view of US Patent No. 4,749,570, Peters (IDS reference "AT") and the known facts disclosed in the specification on page 27 at lines 9-13.

US Patent No. 4,751,286 discloses use of a bridging molecule to attach the reduced disulfide bonds of a monoclonal antibody or fab to a toxin or a drug, and the mAb-bridging molecule-toxin conjugate (especially column 8 at lines 21-26), and the bridging molecule itself may bear a label (especially column 3 at lines 5-8). US Patent No. 4,751,286 discloses the use of the bridging molecule is designed to preserve the native protein structure (especially column 2 at lines 58-61).

US Patent No. 4,751,286 does not disclose an antibody conjugated to albumin wherein the antibody and albumin are indirectly linked by the bridging molecule between the thiol groups of a cysteine residue present in the antibody and another present in the albumin at position 34.

US Patent No. 4,749,570 discloses the conjugation of albumin to therapeutic agents such as antibodies to increase their resistance to bioinactivation (especially column 2).

Peters teaches the presence of a free cysteine in albumin (especially paragraph spanning pages 164 and 165).

The known facts disclosed in the specification on page 27 at lines 9-13 are that serum albumin has one cysteinyl residue that is not engaged in a disulphide bond, i.e., at position 34 in mature human albumin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have conjugated albumin disclosed by US Patent No. 4,749,570 to the antibody conjugate disclosed by US Patent No. 4,751,286 by the cysteine of the monoclonal

antibody as taught by US Patent No. 4,751,286 and the cysteine at position 34 in albumin taught by Peters and the said admissions in the specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce an antibody conjugate as disclosed by US Patent No. 4,751,286 which is more resistant to bioinactivation by coupling to albumin as disclosed by US Patent No. 4,749,570 that retains the native structure of the albumin carrier by non-disruption of intrachain disulfide bonds as taught by Peters and the said admissions in the specification. Claim 17 is included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the Fab at the CH1 carboxy terminus to include the cysteine involved in the interchain disulfide bond of the intact antibody in order to utilize the cysteine in disulfide binding without disrupting intrachain disulfide bonds.

Applicant's arguments in the amendment filed 3/8/04 have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on page 9 (at the last three paragraphs) through page 11.

It is the Examiner's position that US Patent No. 4,751,286 discloses a compound comprising a bridging agent (optionally linked to a drug, dye or label) capable of bridging reduced or unpaired sulfhydral groups of a protein. It is the Examiner's position that US Patent No. 4,751,286 discloses an example of a particular bridging agent, crabescein, and that insertion of this bridging agent across the reduced disulfide bonds in fab fragments of antibodies or the fab region of intact antibodies can alter the affinity (column 8 at lines 33-46). It is the Examiner's position that US Patent No. 4,751,286 discloses that wherein the protein is an intact antibody, the crabescein bridging agent is inserted below the hinge region, a region not present in a fab fragment of an antibody, and that structural analyses of IgGs have shown that unlike the region of the interchain disulfide bond in the Fab segment, below the hinge region there is little interchain interaction between the heavy chains, thus there is a space in this region large enough for a bridging molecule the size of crabescein to enter and reside in (column six at lines 62-67). It is the Examiner's further position that US Patent No. 4,749,570 discloses albumin-F(ab')2 antibody fragments to reduce immunogenicity (Table II at column 7, Example 5). It is the Examiner's position that one of ordinary skill in the art would have been motivated to use a bridging agent capable of bridging reduced or unpaired sulfhydral groups in a protein, and the said agent having the expected property of bridging reduced or unpaired sulfhydral groups of one protein to another protein, the size of the said agent chosen for the purpose for which it is used as disclosed by US Patent No. 4,751,286 to make a fab-albumin-therapeutic agent conjugate using a bridging agent of the general structure disclosed by US Patent No. 4,751,286 (not crabescein) or a F(ab)'2-albumin-therapeutic agent conjugate using crabescein (which inserts at residue cys-229 that is present in F(ab')2 fragments).

It is the Examiner's further position that one of ordinary skill in the art at the time the invention was made would have been motivated to use the free cysteine at position 34 of human serum albumin taught by Peters because it is unpaired, and one of ordinary skill in the art would have been motivated to use albumin in native conformation where an antigen-binding antibody fragment rather than an intact antibody was being used because Peters teaches that albumin in native conformation is an abundant serum protein with a half-life in circulation of about 19 days, similar to that of the IgG isotype antibody (known to one of ordinary skill in the art at the time the invention was made, as evidenced by admitted prior art Waldeman et al 1969 (IDS reference "AZ"), page 3 at lines 14-16 of the instant specification).

It is the Examiner's further position that the claims reciting a linker length of around 10 to around 20 angstroms in length are not included in this rejection

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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August 13, 2004

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